UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/593,316	06/13/2000	John Clark	730/002	5627

22869 7590 12/16/2004

GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/593,316	CLARK ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13-17,22 and 27-37* is/are pending in the application.

4a) Of the above claim(s) *7,17,22 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,13-16 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8/17/04
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

The following documents have been filed since the last Office action mailed 1/30/04:

1. Response to the Office action submitted 7/30/04,

2. Demand for Examiner's Affidavit pursuant to 37 CFR § 1.104(d)(2) submitted 8/2/04;

3. Supplemental response and Declaration under 37 CFR § 1.132 by Ian Wilmut submitted 9/23/04.

The contents of the submission will be addressed in the order they submitted.

No claims have been amended. Claims 1-6, 13-16, and 33-37 are under current examination.

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 33-37 stand rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible asserted or a well-established utility.

In the response of 7/30/04, Applicants first argue that the utility requirement does not depend on whether the specification enables the claimed invention, and ovine tissue devoid of antibody-detectable Galα(1,3) Gal determinants are useful.

In response, utility and enablement are two different provisions of the patent law. According to the Examination Guidelines for Utility Requirement, when a specific utility has been asserted in the specification, claims should be reviewed for the credibility of the asserted utility, which is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertion (Examination Guidelines for Utility Requirement, B, 2 (2), Federal Register. Vol. 66, No. 4, page 1098, published Jan. 5, 2001). Thus, it is necessary to assess the disclosure of the specification and any other evidence of record.

In the instant case, the claims are drawn to ovine tissue and cells devoid of antibody-detectable Galα(1,3) Gal determinants, ovine cells homozygous for inactivation of an α(1,3)GT gene, and an ovine animal homozygous for inactivation of an α(1,3)GT gene. The specification asserts that the tissue and cells could be used for xenotransplantation.

However, none of the claimed subject matter has been materialized at the time of instant filing date. The specification fails to disclose an ovine *heterozygous or homozygous* for α1,3GT inactivation. Without production of a live lamb heterozygous for α1,3GT inactivation, breeding is not reduced since a fetus could not be used for breeding a viable lamb homozygous for α1,3GT inactivation. Accordingly, there is no credible utility for claimed ovine and ovine cells.

It is noted that the Utility guidelines indicates once a rejection of claims under § 101 is made on the grounds that the invention as claimed lacks utility, also reject the claims under § 112, first paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed due to the lack of a specific and substantial utility. This is the basis that both utility rejection and enablement rejection were made.

Applicants then allege that the Office provides no rationale why heterozygous animals would be phenotypically identical to normal animals. Applicants asserted that there would *probably* be a gene dosing effect with only one allele instead of two, the density of Galα(1,3) Gal determinants on the cell surface may be lower. Applicants then pointed to Costa et al, specification, and U.S. patent 5,849,991 as support.

In response, neither the specification nor cited art of record provide evidence that disruption of one allele of Gal α(1,3) GT would reduce the density of Galα(1,3) Gal determinants on cell surface. *Costa et al* teach expressing the human α1,2-fucosyltransferase in pigs for altered cell surface carbohydrate phenotype, *Costa et al* did not teach that disruption of one allele of Galα(1,3) GT would reduce the density of Galα(1,3) Gal determinants on cell surface. The '991 patent teach a homozygous α(1,3) GT knockout mouse made with ES cells, which could not have been done in ovine because the ovine ES cells have not been isolated and did not teach a gene dosing effect. The specification teaches an assay for detecting the presence and density of Galα(1,3) Gal determinants, but it does not teach a gene dosing effect. More importantly, the specification as originally filed only contemplates that the heterologous knockout cells could be used for further knockout of the second allele. The specification

as originally filed fails to teach a gene dosing effect due to the disruption of one allele of the α1,3GT gene.

In fact, applicants acknowledged that the heterologous knockout would not meet the phenotypic limitation of the claimed invention. In the response filed 3/19/2002, Applicants stated, "the expression of the Galα(1,3) Gal epitope is autosomal dominant. The skilled reader will readily appreciate why this is so" (1st, paragraph, page 4), "Accordingly, Galα(1,3) Gal will only be absent if the cells don't express any Galα(1,3) GT--i.e. the Galα(1,3) GT gene must be inactivated on *both* haplotypes. A cell or animal that is inactivated for Galα(1,3) GT on just one allele will still have Galα(1,3) Gal on their cells at a density that would often still be antibody detectable, and a potential problem for xenotransplantation" (2nd paragraph, page 4, emphasis added). Further, the publications of *Lai* and *Dai et al* showed there is a genotype change in the heterozygous α1,3GT knockout pigs, they did not show any phenotype change. Accordingly, it is apparent that the rationale has been clearly provided by the applicant and the knowledge of the skilled in the art.

Applicants go on to argue that the heterozygous Galα(1,3) GT knockout animals have utility for making homozygous knockout animals by crossbreeding or targeting the second allele.

In response, the heterozygous Galα(1,3) GT knockout animals have not been produced. Moreover, materials to be used for research, or methods of using those materials for research, raise issues of whether the utilities require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. See, e.g., Brenner v. Manson, 383 US 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a

research utility was not considered a "substantial utility". In the instant case, since the asserted utility of heterologous knockout cells involves further research and development, and the heterozygous α1,3GT knockout sheep has not been produced, the asserted utility is not specific and substantial.

With respect to targeting the second allele of a heterozygous α1,3GT cell, Applicants cited Phelps et al and Kolber-Simonds et al as support. However, as indicated in the previous Office action, these post-filing date references further support the lack of enablement for the means of targeting the second allele as taught in the specification (See discussion under 35 USC § 112, 1st paragraph). Based on the methods taught by the specification, the skilled in the relevant art has failed to achieve disrupting the second allele of α1,3GT gene for any species of farm animals at the time of the instant priority date or at a post-filing date. The pigs having homozygous α1,3GT inactivation are made long after the effective filing date, and are both produced by cells bearing a mutation on the second allele of the α1,3GT gene selected with an innovative method. Thus, from the experience in the pig, it would have required additional knowledge generated after the instant effective filing date to achieve the claimed invention. Since as of today, the record is silent with respect to a heterozygous or homozygousα1,3GT knockout sheep, the specific utility of the claimed subject matter could not be evaluated, and hence in view of the state of the art and the instant disclosure, the asserted utility is not considered credible.

Accordingly, it is maintained that the claimed invention is not supported by a substantial asserted utility, a creditable asserted utility, or a well-established utility for the reasons set forth on record and above.

Claims 1-6 and 33-37 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and those set forth *supra*.

ENABLEMENT REQUIREMENT

Claims 1-6, 13-16, and 33-37 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants summarized the previous Office action, and presented arguments accordingly. Although the summary is not entirely accurate, the arguments will be addressed in the order they presented.

1. Working Example:

Applicants asserted that the methods of inactivating genes by homologous recombination and nuclear transfer are both well known in the art, the specification discloses the sequence of sheep α1;3GT gene needed to create α1,3GT knockouts as has been done for other species, it is not necessary to provide the working example,

and the Office has not explained exactly what information is missing that is required to carry out the invention.

In response, Applicant's attention is directed to the Office actions on record, particularly pages 5-12 of the Office action mailed 1/30/04, wherein the Office cited numerous art of record to illustrate the state of the art and unpredictability in the art. This is because "WHETHER UNDUE EXPERIMENTATION IS NEEDED IS NOT A SINGLE, SIMPLE FACTUAL DETERMINATION, BUT RATHER IS A CONCLUSION REACHED BY WEIGHING MANY FACTUAL CONSIDERATIONS." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). MPEP states, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) In the instant case, since many factual evidences point toward a lack of enablement for the claimed invention, lack of a working example is a factor to be considered against enablement.

It is noted however, lack of working examples is not the basis for the conclusion for lack of enablement in this application. The Office acknowledged that the specification does disclose working examples showing the attempts of making heterozygous α (1,3)GT knockout fetus. However, the applicant fails to bring the fetus to term, and fails to obtain what is claimed at the time the instant application was filed. The Office has cited numerous art of record such as *Yanagimachi and Wells et al* indicating that the phenomenon is not just accidental but reflects the real difficulty and challenge in animal cloning. Accordingly, what is missing in the specification is the sufficient

guidance concerning how to overcome the unpredictability in the art so that one skilled can practice the invention without carrying out undue experimentation.

2. The Art of Nuclear Transfer:

Applicants first argue that the cited articles of Donovan et al and Simerly et al are drawn to humans and other primates, not sheep.

In response, it is noted the *Donovan et al* and *Simerly et al* references were not part of the original rejection under this provision, but used later on when addressing arguments presented by the applicants. It is inappropriate that Applicants decided to ignore the numerous cited art of record concerning nuclear transfer, such as *Yanagimachi, Well, Phelps,* and an article written by the applicants specifically addressing the difficulties for somatic cell nuclear transfer in the sheep (*Denning et al*), and chose to attack references used for addressing other issues.

Concerning the references of *Donovan et al* and *Simerly et al*, they were cited when discussing the efficiency of ES cells on animal cloning compared to somatic cells. Since the ES cells have yet to be available in ovine, these references were used to evidence the differences between mouse and primate ES cells, and the unpredictability on the characteristics of the ES cells among mouse, human, and possibly farm animals, which ES cells are yet to be isolated.

Applicants then cited numerous issued U.S. patents arguing the position of the Office is inconsistent. In response, the court (*In re Giolito and Hofmann*, 188 USPQ 645 (CCPA 1976)) states, "IT IS IMMATERIAL WHETHER SIMILAR CLAIMS HAVE BEEN ALLOWED TO OTHERS. SEE IN RE MARGAROLI, 50 CCPA 1400, 318 F.2D 348, 138 USPQ 158 (163); IN RE

WRIGHT, 45 CCPA 1005, 256 F.2D 583, 118 USPQ 287 (158); IN RE LAUNDER, 41 CCPA 887, 212 F.2D 603, 101 USPQ 391 (1954)." Each application is examined on its own merits and cannot be compared to other application.

Applicants go on to cite numerous post-filing art as successful reports of cloning genetically altered animals.

However, the references are not completely analogous for the claimed subject matter. This is because most of the cited references are not drawn to knockout animals, and all of the cited references are directed to different animal species, different genes, and each success has a unique story. Moreover, out of 15 references cited, only two references are published *before* the effective filing date, both of which are drawn to a transgenic not knockout animal. For example, *Uchida et al* reference is a post-filing art, drawn to a transgenic miniature pig, not a knockout sheep. Without going into the details, *Uchida et al* stated at the post-filing date, "THIS STUDY IS THE FIRST SUCCESSFUL REPORT CONCERNING THE PRODUCTION OF TRANSGENIC MINIATURE PIG BY PRONUCLEAR MICROINJECTION" (abstract), which illustrated the state of the art, i.e. successful production of transgenic miniature pig by pronuclear microinjection has not yet been achieved at the time of instant priority date, and that it is not routine in the art to produce the claimed invention. *Bondoli et al* is a post-filing date reference, drawn to transgenic pigs, not a knockout sheep. *Lai et al* reference is a post-filing date art, drawn to a transgenic pig, not a knockout sheep. *McCreath et al* is a post-filing date reference describing the efficiency of reproductive gene insertion in sheep, not a knockout sheep. Without going into the details, *McCreath et al* also stated at the post-filing date, "THE

GENE TARGETING HAS NOT YET BEEN ACHIEVED IN MAMMALS OTHER THAN MICE", which again illustrated that it is not routine in the art to produce the claimed invention. *Dai et al,* and *Lai et al* reported at a post-filing date a knockout *pig* that is *heterozygous* for α (1,3)GT gene, not homozygous sheep. Likewise, more than four years after the effective filing date, *Sendai et al* reported the *first* success of *heterozygous* disruption of the α (1,3)GT gene in cattle. It is noted the genetic background differs among sheep, pig, and cattle. As indicated in the specification, pig and sheep share 90% and 82% homology in nucleic acid and amino acid sequences respectively (Specification, table 1). Although these may not appear to be huge differences, the fact is what has been achieved in pigs and cattle at a post-filing date has not been achieved in sheep even though attempts have been made in altering α (1,3)GT gene in sheep. The disclosure of *Denning et al* is another post-filing date publication that is similar to instant disclosure, which further demonstrated the unpredictability in the art. *Denning et al* obtained live birth of sheep having a deletion in PrP gene but not those having a deletion in α (1,3)GT gene. This indicates that cloning efficiency differs between cloned sheep having different target genes and the targeting gene is relevant to the success of reproductive cloning. With respect to the *Phelps* reference, it has been discussed in detail in the last Office action (pages 9-10), and it has confirmed that the method taught in the instant disclosure would not be successful in knocking out the second allele of the α (1,3)GT gene in pigs. As for the *Kolber-Simonds* reference, like the *Phelps et al* reference, *Kolber-Simonds* teach that the α (1,3)GT null pigs were produced by means of nuclear transfer with fibroblasts bearing *mutation* on the second allele of the α (1,3)GT gene, it is *not* the

result of genetic targeting of the second allele. *Dor et al* conducted further research on the available α (1,3)GT null pigs five years after the instant filing date, and it does not support the enablement of the instantly claimed invention.

Applicants also requested the attention to *Schnieke* and *Cibelli* references. *Schnieke et al* reported a transgeneic sheep, and *Cibelli et al* reported cloning bovine. However, because of the unpredictability in the art, these successes in cloning could not sufficiently support the enablement of instantly claimed invention because cloning has not become routine in the art and is not the only barrier to produce the claimed sheep.

It is noted *Kuroiwa et al* reported a sequential gene targeting method for making homozygous Ig-μ gene knockout cattle. *Kuroiwa* reference deserves attention because they gave a clear review regarding the state of the art in animal cloning. *Kuroiwa et al* teach breeding to homozygosity is severely impeded in species that have a long generation interval, such as cows, sheep and pigs, further they are negatively impacted by the consequences of inbreeding. *Kuroiwa et al* particularly mentioned "innovative" approaches to obtain homozygous α (1,3)GT knockout pigs such as reported by *Phelps et al*, but pointed out "UNFORTUNATELY, THESE APPROACHES ARE NEITHER USEFUL FOR SILENT GENES NOR WIDELY APPLICABLE FOR ACTIVE GENES" (right column, page 775). The success of *Kuroiwa et al* was brought about by another innovative approach, i.e. sequential application of gene targeting by homologous recombination and rejuvenation of cell lines by cloned fetuses. Such approach was developed long after the instant filing date, and the specification fails to teach such a method, thus, the reference does not support the enablement of instant claimed invention. To the contrary, it confirms that it requires

further development and undue experimentation to enable the instantly claimed invention. As for the *Ramsoondar* reference, they reported using a specific construct targeting a specific region of the α (1,3)GT gene of cattle, and as of the publication date (4 years after the instant effective filing date), only heterozygous knockout was achieved. Assuming a homozygous knockout of the α (1,3)GT gene in cattle could be achieved later, the specific method which leads to the success was not taught in the instant disclosure.

From above analysis, it has become apparent that applicants have constantly rely on post-filing date references as support for enablement of the instant claimed invention. This is inappropriate. Applicants are reminded that the court has stated (*In re Glass*, 181 USPQ 31, (CCPA 1974)), IF A DISCLOSURE IS INSUFFICIENT AS OF THE TIME IT IS FILED, IT CANNOT BE MADE SUFFICIENT, WHILE THE APPLICATION IS STILL PENDING BY LATER PUBLICATIONS WHICH ADD TO THE KNOWLEDGE OF THE ART SO THAT THE DISCLOSURE, SUPPLEMENTED BY SUCH PUBLICATIONS, WOULD SUFFICE TO ENABLE THE PRACTICE OF THE INVENTION. INSTEAD, SUFFICIENCY MUST BE JUDGED AS OF THE FILING DATE; SECTION 132 PROHIBITS ADDING NEW MATTER TO DISCLOSURE AFTER FILING" (Emphasis added). In *In re Glass*, the appellant attempted to use the disclosures of four patents issued after his filing date, and court ruled, "IF INFORMATION TO BE FOUND ONLY IN SUBSEQUENT PUBLICATIONS IS NEEDED FOR SUCH ENABLEMENT, IT CANNOT BE SAID THAT THE DISCOSURE IN THE APPLICATION EVIDENCES A COMPLETED INVENTION... IT IS AN APPLICANT'S OBLIGATION TO SUPPLY ENABLING DISCLOSURE WITHOUT RELIANCE ON WHAT OTHERS MAY PUBLISH AFTER HE HAS FILED AN APPLICATION ON WHAT IS SUPPOSED TO BE A COMPLETED INVENTION", "IF HE CANNOT SUPPLY ENABLING INFORMATION, HE IS NOT YET IN A POSITION TO FILE". In the instant case, applicants

heavily relied on α (1,3)GT null pigs that become available four years after the instant filing date for enablement of the claimed invention on a sheep. However, none of the post-filing success in α (1,3)GT null pigs could be achieved in the absence of further advance in knowledge and technology of animal cloning that become available after instant filing date. Thus, judged as of the filing date, the instant disclosure is insufficient to provide enablement for what is claimed.

Applicants then concluded the following:

1). Pigs, cattle, and sheep can all be cloned by the Campbell and Wilmut method using genetically altered donor cells to make genetically modified animals.

In response, it is noted the technology for making genetically modified animals have undergone significant development, new techniques and knowledge have emerged since the *Campbell and Wilmut* patent, without such progress, the homozygous pig disclosed by *Phelps* or the cattle disclosed by *Kuroiwa et al* would not have been obtained. Moreover, none of the references appear to disclose a cloned knockout sheep.

2). Cells can be genetically modified and cloned by nuclear transfer through at least five cycles.

In response, it is unclear how this relates to the enablement of instant claimed invention, and this fact alone would not lead to the success of the homozygous knockout of the α (1,3)GT gene.

3). α (1,3)GT knockout fetuses have been produced by nuclear transfer in three different species.

In response, applicants are reminded that the homozygous knockout mice are produced with ES cells, which are much more efficient in cloning compared to somatic cells, and are not available for other animal species. Attempts for making heterozygous α (1,3)GT gene inactivation have been made but failed in sheep and pig at the time of the instant filing date (*Denning*, Cloning & Stem Cells 2001;3:221-31), and the claims are drawn to homozygous knockout sheep.

4). Non-isogenic targeting constructs have been used successfully to make α (1,3)GT gene knockout pigs and IGHM knockout cattles.

In response, Applicants are reminded that only the heterozygous α (1,3)GT knockout pigs have been successfully made with the non-isogenic targeting constructs. The homozygous disruption in pigs is the result of a mutation on the second allele, not made by a targeting construct. The IGHM knockout cattle were made by an innovative method, which is not taught by the specification.

5). Homozygous knockouts of any one of several genes can be made without difficulty by harvesting cells from heterozygous animals or fetuses, inactivating the second allele, and then doing a second round of nuclear transfer.

In response, out of the fifteen references cited by the applicants only two genes are the subject of knockout, i.e. the α (1,3)GT gene and the IGHM gene. These knockouts were made long after instant filing date, and succeeded not in the sheep species. When reporting the success of sequential targeting of the IGHM gene in the Journal of Nature Genetics, *Kuroiwa et al* teach, "GENE TARGETING IN SOMATIC CELLS VERSUS EMBRYONIC STEM CELLS IS A CHALLENGE; CONSEQUENTLY, THERE ARE FEW REPORTED

SUCCESSES AND NONE INCLUDE THE TARGETING OF TRANSCRIPTIONALLY SILENT GENES OR DOUBLE TARGETING TO PRODUCE HOMOZYGOTES" (emphasis added). This is the assessment of the skilled artisan with respect to the state of the art in animal cloning at more than four years after instant effective filing date. Accordingly, it appears that the applicant's assessment here is far off from the cited skilled in the art. Further, when looking into the details, the post-filing date achievement was not a simple routine experimentation; it was achieved by significant discovery and progress in cloning technology after the instant disclosure (e.g. *Phelps et al*). In fact, applicants provide a different assessment at after the effective filing date, which is consistent with the assessment of *Kuroiwa et al.* This assessment can be seen in the teaching of the applicants, see *Denning et al* (Cloning & Stem Cells 2001;3:221-31), which reads "SIGNIFICANT CHALLENGES, SUCH AS ESTABLISHMENT OF SOMATIC GENE TARGETING TECHNIQUES, MUST BE OVERCOME BEFORE THE TECHNOLOGY CAN BE APPLIED ROUTINELY" (abstract), "WE EXPERIENCED SIGNIFICANT PROBLEMS IN ISOLATING POPULATIONS THAT COULD BE USED FOR NT" (last paragraph, page 229), "THEREFORE, IT IS DIFFICULT TO IMAGINE HOW IT WILL BE POSSIBLE TO ISOLATE SUCH LINES FROM NORMAL PIG FIBOBLASTS SUCH AS THESE WITH THE FREQUENCIES OF GENE TARGETING THAT WE REPORT" (1st paragraph, page 230), and "THERE IS CLEARLY A NEED TO OPTIMIZE AS WELL AS DEVELOP NEW APPROACHES IN BOTH SPECIES" (last paragraph, page 230). Clearly, these published teachings contradict the above conclusion, "Homozygous knockouts of any one of several genes can be made without difficulty".

6). Homozygous α (1,3)GT gene knockout cells can be readily made and identified by several different techniques.

In response, according to the discussions of record and *supra*, this does not appear to be true for the state of the art at the time of instant filing date. Several post-filing date references provided by the applicants and publications by the applicants have shown further progresses are required for the success. Applicants are reminded that the enablement or lacking thereof is judged as of the effective filing date.

7). Two independent groups have successfully made homozygous α (1,3)GT gene knockout pigs, which are healthy and essentially free of the α (1,3)Gal antigen.

In response, Applicants are again reminded that such have been achieved at a post-filing date, and not by successful targeting of the second allele, but by a mutation selected with the advance in selection technique, which was not taught by instant specification.

Therefore, it is concluded that a doubt is reasonable for making the claimed homozygous sheep at the time of instant effective filing date. It would have required undue experimentation for the skilled intending to practice the claimed invention at the time this application was filed.

3. Phenotype of α (1,3)GT knockouts:

This is not an issue once a homozygousα (1,3)GT gene knockout animal is made. As discussed previously and *supra* the matter at issue is whether it requires undue experimentation to make such sheep at the instant effective filing date, and without further development of cloning technology (undue experimentation).

4. Purported Lethality of α (1,3)GT gene knockouts:

Applicants objected a statement in the Office action "the α (1,3)GT gene disruption kills the (sheep) fetus" as "without foundation".

In response, Applicants are reminded although from hindsight view based on the information that become available after the instant filing date, one has better understanding as to why the cloned fetus died, just reading the specification, it is easy to make above conclusion because it is an undeniable fact that the cloned ovine fetuses survived the disruption of PrP gene, but not heterozygous α (1,3)GT gene inactivation. It is the experience of applicants that evidenced the inability to produce a sheep having the heterozygous disruption of the α (1,3)GT gene.

On the other hand, the Office also provided the teachings of the skilled in the art (*Yanagimachi et al,* 2002 and *Wells et al,* 2003) indicating that the high death rate in cloned animals reflects the difficulties in cloning technology and is attributed to faulty epigenetic reprogramming of the donor cell genome. This evidenced the full opinion of the Office that both the target gene related factors and the state of the cloning technology contributed to the death of the fetus.

Applicants then propose that the fetus did not reach to term *may be* attributed entirely to the low efficiency of cloning, and it is a matter of routine repetition. However, the proposal itself reflects the uncertainty in the relevant art, because a simply repetition may or *may not* lead to the success. And according to the teaching of *Phelps et al, Kuroiwa et al, Yanagimachi et al* and *Wells et al,* further development and understanding of cloning technology is necessary to the final success. Applicants are reminded "LAW REQUIRES THAT THE DISCLOSURE IN APPLICATION SHALL INFORM THOSE SKILLED IN

THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT HOW TO FIND OUT HOW TO USE IT FOR THEMSELVES" *In re Gardner* 166 USPQ 138 (CCPA) 1970. In view of numerous teachings cited illustrating the state of the art and the knowledge of the skilled in the art at the time of the effective filing date, coupled with the guidance provided in the specification, it is concluded that the specification fails to provide an enabling disclosure for the claimed invention.

Claim 16 stand rejected for reasons of record and because it is drawn to a method of xenotransplantation using ovine tissue devoid of antibody detectable Gal(1,3)Gal determinants. As discussed foregoing, the specification fails to provide sufficient guidance or reduced to practice to provide the claimed ovine homozygous for α1,3GT gene inactivation, thus, the starting material for the claimed method is lacking and hence the method is not enabled.

Applicants argue that the xenogenic rejection could be resolved by other means such as immune suppression. Applicants cited art of record for xenogeneic heart valve replacement surgery as supporting evidence.

In response, as an initial matter, the claimed method is not for any xenogenic transplantation, but for xenogenic tissue lacking Gal α (1,3)Gal determinants, thus the response citing other xenogenic transplantation is not really addressing the rejected subject matter. Nevertheless, it is noted that the heart valve in the cited references were treated with glutaraldehyde or buffered acid formaldehyde to eliminate the antigenecity of the tissue, this can be done in a thin tissue layer such as heart valve as described in

the articles. This cannot be done for a whole organ or larger tissue, wherein the function of the organ and tissue may be depleted by such fixation/preservation.

What applicants have not and cannot argue is that the starting materials required for practice the claimed invention of claim 16 have yet to become available at the time of the filing date, and at more than four years after the effective filing date, thus, the skilled intending to practice the invention has to first carrying out undue experimentation to make the required homozygous knockout sheep.

As to the immunosuppression therapy, it is noted that *Platt et al,* as skilled artisans, are fully aware of the immune suppression therapy known in the art. Therefore, when *Platt et al* (Nat Biotech 2002 Mar;20(3)231-2) concluded; "UNFORTUNATELY, SOLVING THE PROBLEM OF HYPERACUTE REJECTION DOES NOT MAKE XENOTRANSPLANTATION FEASIBLE, BUT RATHER REVEALS A MORE VEXING PROBLEM CALLED ACUTE VASCULAR REJECTION" in a prestige journal at a post-filing date, it implies that the routine immune suppression could not overcome the immune rejection mounted by a host against xenogenic organs lacking Gal α (1,3)Gal determinants.

Accordingly, in view of the limited guidance, the lack of predictability of the art and the nature and breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Demand for Examiner's Affidavit

Applicants requested an affidavit from the Examiner because there is a sentence in the Office action, which reads "the α (1,3)GT gene disruption kills the fetus".

Applicants concluded that there is no evidence supports the conclusion and the contention is drawn from the personal knowledge of the Examiner.

In response, the sentence is not the complete opinion of the Examiner nor derived from the personal knowledge of the Examiner. Thus, it is not necessary to provide an Examiner's affidavit.

As discussed foregoing, at least from the first glance of the specification, it appears that the cloned ovine fetus survived PrP gene disruption, but not the α (1,3)GT gene disruption. Only when more factual evidence become available at a post-filing date, one would realize from hindsight view that cloning process may be another important and even more troublesome factor contributing to the failure of obtaining the live birth of fetus having a disrupted α (1,3)GT allele, such evidence are apparent in the cited *Yanagimachi et al and Wells et al,* and now in the newly submitted declaration of Dr. Wilmut,

Declaration of Dr. Wilmut

Dr. Wilmut concluded that the failure of the α(1,3)GT knockouts was not attributable to the genetic modification, rather, it reflects the rate of failure in this series of experiments, irrespective of what genetic modification were made.

In response, this may be true for the incidence of lung vascular abnormality, but may not reflect the whole picture of gene inactivation and cloning process. It is noted that indeed, the *Rhind* reference has shown that genetically manipulated cloned animals do not have higher incidence of lung vascular disease that may be fatal compared to

cloned animals without the genetic manipulation. The study reflects one factor contributing to the death of the cloned fetus; it however does not exclude other factors in genetic manipulation that may cause the failure of the cloning process for α(1,3)GT knockouts. More importantly, the Office maintains the disclosure fails to provide an enabling disclosure because it fails to teach how to overcome the hurdles known in the art whether it is caused by genetic modification or by cloning technology.

Dr. Wilmut then states there is no reason why genetically modified animals cannot be made according to the method of Keith Campbell described in our patent disclosure, and concluded "it is my believe that culture cell lines such as those used by Denning et al. will successfully generates cloned animals after sufficient persistence". He continued by referring to the post-filing publications of *Phelps et al, Kolber-Simonds et al, and Kuroiwa et al* as the support for his believe.

In response, since cloning with the cell lines used by *Denning et al* (Nature Biotech) has not been materialized for production of a homozygous α (1,3)GT knockout ovine, the Office can not evaluate the enablement solely based on the *believe*, rather the Office turn to the factual evidence in the cited post-filing publications for additional information. To this end, *Kuroiwa et al, Phelps et al,* and *Denning et al* (Cloning & Stem Cells) all teach that further development of the cloning technology is necessary for the success of cloning a null animal. Since the instant specification fails to teach the innovative approaches taught by *Phelps et al, Kolber-Simonds et al, and Kuroiwa et al,* a reasonable conclusion was reached after weighing many factual considerations that the specification fails to provide the information necessary for success in ovine.

Dr. Wilmut goes on to state "the cloning method used by all these groups is the same as described by Campbell and Wilmut patents. There is no modification to any aspect of our method".

In response, this conclusion is contradictory to the teaching of *Kuroiwa et al*, who named the approaches of *Phelps* and his own work as innovative, this conclusion is also contradictory to the publication of *Denning and Clark*, who calls for further development in somatic cell targeting and cloning technology, "WE EXPERIENCED SIGNIFICANT PROBLEMS IN ISOLATING POPULATIONS THAT COULD BE USED FOR NT" (last paragraph, page 229), "THEREFORE, IT IS DIFFICULT TO IMAGINE HOW IT WILL BE POSSIBLE TO ISOLATE SUCH LINES FROM NORMAL PIG FIBOBLASTS SUCH AS THESE WITH THE FREQUENCIES OF GENE TARGETING THAT WE REPORT" (1st paragraph, page 230), and "THERE IS CLEARLY A NEED TO POTIMIZE AS WELL AS DEVELOP NEW APPROACHES IN BOTH SPECIES" (last paragraph, page 230). At the least, *Phelps* employed a new selection method, which was not taught by *Campbell* patent or instant specification, "BECAUSE WE USED THIS POWERFUL SELECTION METHOD, WHICH ALLOWS US TO ISOLATE ANY EVENT THAT RESULTS IN LOSS OF α1,3GT ACTIVITY, WE DISCOVERED A MUTATION IN THE SECOND ALLELE OF THE α1,3GT GENE. HAD WE USED STANDARD SELECTION METHODS WITH PUROMYCIN OR HYGROMYCIN, WE WOULD NOT HAVE FOUND THE MUTATION" " (right column, page 413, emphasis added). *Kuroiwa et al* also disclosed a new approach that rejuvenates the cell lines by cloned fetuses. Apparently, the art of record evidenced the cloning technology originated from the Campbell and Wilmut patent has undergone significant development.

Accordingly, the declaration is not persuasive in view of numerous teachings of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

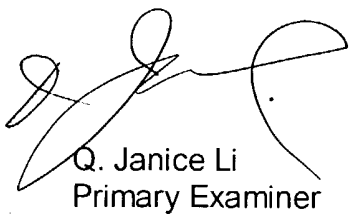
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Q. Janice Li
Primary Examiner
Art Unit 1632

QJL
December 8, 2004